UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,585	03/04/2002	Esa-Matti Lilius	2328-124	6319

6449 7590 11/06/2003

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
FIELD, TAMMY K	

ART UNIT	PAPER NUMBER
1645	9

DATE MAILED: 11/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,585	LILIUS ET AL.	
	Examiner	Art Unit	
	Tammy K. Field	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Applicant is entitled to the priority date of June 7, 1999.

Information Disclosure Statement

2. The information disclosure statement filed 4 December 2001 has been considered. An initialed copy is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method to enable the assessment of the growth rate and death rate of a micro-organism that contains in a plasmid one reporter gene coding for a luminescent

product (luciferase fluorescent product) used for the determination of the amount of cells alive at any moment and another reporter gene (Green Fluorescent Protein or GFP) used for the determination of amount of cells that are or have been alive. Further claims are drawn to said microorganism plasmid containing pGFP+luc* (SEQ ID: 1).

In claim 1, "said reporter genes code for luminescent and/or fluorescent products" indicate reporter genes code for both luminescent and fluorescent products or one of the products alone. The teachings of the specification are limited only to the use of pGFP+luc together in a plasmid of *E.coli*.

The specification is not enabled for other groupings of reporter genes such as taught by Grentzmann *et al.* (US Patent No. 6,143,502 published 7 November 2000) where two different luciferase genes (i.e. sea pansy and firefly) producing luminescent products were used before and after test DNA in a plasmid translational reporter system to measure luminescences attributable for each of the translation products at column 3 lines 26-60. Grentzmann *et al.* further uses controls at column 3, line 61 – column 4, line 3.

In the Brief description of the Drawings of the instant specification in Figures 6 and 7 are diagramed fluorescence and luminescence, respectively before and after incubation with serum complement during growth phase of E. coli with plasmid pGFP+luc* at 30° C as a function of the concentration of serum complement in the cell culture. Lines indicated by circles versus squares in both figures are unclearly described as to which is before or after incubation.

4. Claims 1-10 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1 a) i), the language of "an essentially stable product in a" is unclear and

without descriptive language fully explaining its meaning in the specification is considered indefinite.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1-4, and 6-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Szalay *et al.* in US Patent 5,976,796 published 2 November 1999.

The claims are drawn to a method to enable the assessment of the growth rate and death rate of a micro-organism that contains in a plasmid one reporter gene coding for a luminescent product (luciferase fluorescent product) used for the determination of the amount of cells alive at any moment and another reporter gene (Green Fluorescent Protein or GFP) used for the determination of amount of cells that are or have been alive. Further claims are drawn to said microorganism plasmid containing pGFP+luc* (SEQ ID: 1).

Szalay *et al.* teach a method of monitoring gene expression quantitatively and qualitatively in a cell using a gene fusion construct coding for a polypeptide having both luciferase and GFP activities by measuring luciferase and fluorescent activity at column 2, line 63 – column 3, line 17. More specifically, both luciferase and GFP genes were placed into prokaryotic pGEM-5zf(+) of *E. coli* through transformation at column 4, lines 54-56 (see Fig. 3). Fig. 5A disclose photomicrographs of cells transformed by fusion genes using fluorescence microscopy and fluorescence imaging to show GFP activity and Fig. 6A disclose bar graphs of luciferase activity before and after promoter induction of fusion gene constructs of E. coli at column 3, lines 47-51. GFP and luciferase activities were measured following a 12 hr incubation period using inverted fluorescent microscope for GFP activity and luminometer for luciferase activity at column 5, line 62 – column 6, line 11. Since measurements were indicative of either luciferase or fluorescence of actively growing cells in culture, the cells measured were either alive at any moment, are or have been alive when tested.

Since the office does not have the facilities for examining and comparing applicants' methods of growth rate and death rate of a microorganism with the methods disclosed in the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed

methods and the methods of the prior art (*i.e.* that the methods of the prior art does not possess the same material structural and functional characteristics of the claimed methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Fratamico, P.M. *et al.* 1997. (J. Food. Protection. 60(10): 1167-1173 and further in view of Brovko, L.Y. *et al.* 2000. (Proceedings of SPEI - The International Society of Optical Engineering. 3921:147-156) and Wang Y. et al. 1996. (Pro. 9th Int. Sym. on Bioluminescence and chemiluminescence, pages 419-422).

The claims are drawn to a method to enable the assessment of the growth rate and death rate of a micro-organism that contains in a plasmid one reporter gene coding for a luminescent product (luciferase fluorescent product) used for the determination of the amount of cells alive at any moment and another reporter gene (Green Fluorescent Protein or GFP) used for the determination of amount of cells that are or have been alive. Further claims are drawn to said microorganism plasmid containing pGFP+luc* (SEQ ID: 1).

Fratamico, P.M. *et al.* teach the claimed invention limitations of using E. coli O157:H7 strains expressing the reporter genes of the firefly luciferase and GFP and their use in survival studies at page 1169, Results (see Figure 1). Growth kinetics of recombinant and parent strains,

stability and characteristics of bioluminescence, and survival of gfp-1 and gfp-29 of E. coli in apple cider and orange juice during a 25 day period were determined at pages 1170-1171 and Figure 5. Fratamico, P.M. *et al.* differ from applicants' instant claims in that the luciferase and GFP were not on the same plasmid, but instead on different plasmids in the recombinant strains of E. coli.

Brovko, L.Y. *et al.* teach the claimed invention limitations of using E. coli containing a plasmid carrying at least two reporter genes at page 148, Detection of in vivo fluorescence and bioluminescence. A method of assessment if the growth rate and death rate of a microorganism within a chosen time period of an E. coli plasmid carrying five bioluminescent genes (luxCDABE) is taught at page 150, Detection of bacteria tagged with genes for bacterial bioluminescence. The bioluminescent signal depended on metabolic state and growth stage of the cell reaching maximum intensity at the log-stage of growth in the environment of rich nutrient media (TSB) compared with cells suspended in PBS (Fig. 6b). The bioluminescent signal was taught as very stable (Fig. 5). More specifically, the teachings of Brovko, L.Y. *et al.* identify *E. coli* 0157:H7 carrying the firefly luciferase where in vivo bioluminescence was measured ranging from 0-30 minutes under varying pH at page 153, Figure 7. Brovko, L.Y. *et al.* also teach the use of GFP in *E. coli* to determine cell concentration during growth, but differ as with Fratamico, P.M. *et al.* in that both Luciferase and GFP are not located on the same plasmid. Brovko, L.Y. *et al.* use of a five gene construct of luciferase reporter genes does suggest that construction of different dual or multiple reporter gene systems to measure the growth and death of cells in *E. coli* is possible. Brovko, L.Y. *et al.* do not teach the use of

dependent limitation of the reporter genes of luciferase and GFP together on the same microorganism plasmid construct.

Wang, Y. *et al.* teach the use of a cDNA of GFP linked to a bridging peptide of 9 amino acids in length followed by 5' end of Renilla cDNA (GR cassette) and placement into a prokaryotic expression vector pGEM-5zf(+) p at pages 420-421 (see Figure 1). Analysis of both GFP and Luciferase activity before and after induction were measured in *E. coli* cells at page 421 (see Figure 2 a and c). Cells measured after 12 hr incubation at page 420, were inherently alive or alive at any moment. Wang, Y. *et al.* do not teach the limitation of assessment of the growth and death rate of a microorganism.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute the limitations of Fratamico, P.M. *et al.* and Brovko, L.Y. *et al.* in the teachings of methods of assessing the growth rate and death rate of a microorganism with either Luciferase or GFP with Wang, Y. *et al.* that teach the use of a prokaryotic expression vector containing GFP and Luciferase. Thus, Fratamico, P.M. *et al.* and Brovko, L.Y. *et al.* combined with Wang, Y. *et al.* render obvious the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Status of the Claims

7. No claims are allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tammy K. Field whose telephone number is (703) 305-4447. The examiner can normally be reached on Monday-Friday from 7am-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909.

Papers relating to this application may be submitted to Technology Center 1600 Group 1640 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TKF
Tammy K. Field
October 27, 2003

478
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600